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Project Summary

Interaction of Acid Sulfates and the Respiratory System

D. Covert, M. Morgan, T. Larson, W. Frank, N. Horike, D. Holub

Acidic sulfate compounds constitute a large fraction of the mass of sub-micrometric aerosol particles in polluted air. This has prompted extensive research into the health effects of sulfuric acid (H_2SO_4) and its neutralization products with ammonia (NH_3). The research summarized here covers three aspects of the interaction of acidic sulfate aerosols with the respiratory system.

The extent of neutralization of inhaled H_2SO_4 aerosol by endogenous NH_3 has been measured in the surgically isolated upper airways of anesthetized dogs. Neutralization was observed to be inversely proportional to particle size. H_2SO_4 particles with initial dry diameters of 0.5 μm and 1.0 μm underwent 0.28 (0.08) and 0.06 (0.06)% neutralization per ppb of laryngeal NH_3 respectively during passage through the mouth and out the larynx at a flow of 0.1 l/sec. At a given particle size neutralization is related to both the route of entry and the flow rate. It is greater for entry via the mouth than the nose and greater for a flow of 0.1 l/sec than 0.2 l/sec. These results are consistent with a reaction that is limited by the rate of NH_3 diffusion to the particle's surface.

The respiratory response of the guinea pig when exposed to sulfate or histamine aerosols was measured. The response of the guinea pig to histamine aerosol is described as a positive control for future animal exposure studies. Dynamic lung compliance exhibited a progressive decrease during ten-minute exposure to

an aerosol mass concentration of 885 $\mu g/m^3$; those guinea pigs that responded to a lower concentration of 565 $\mu g/m^3$ exhibited the same progressive decrease in compliance. This observation is consistent with the hypothesis that a fraction of any guinea pig population is hypersensitive. Comparisons with the findings of other investigators is made. These data will be used as an index of sensitivity of our biological preparations in the study of pulmonary functional response of guinea pigs to sulfur compounds in atmospheric aerosols.

The potential for ammonia produced naturally in the mouth to modify the effects of inhaled sulfuric acid aerosol particles was investigated in healthy adults. If significant chemical neutralization were to occur before deposition the irritant potency of the aerosol might be significantly reduced. For acid particles with a mass median diameter of 0.65 μm , at the concentration of 500 $\mu g/m^3$, neutralization should have been nearly complete during quiet mouth breathing. This situation was compared to moderate exercise where neutralization should be greatly reduced. Using standard measurements of lung mechanical function and a measure of density dependence of expiratory flow, there was evidence for mild constriction of small airways when exposure occurred during intermittent exercise. The effect of acid aerosol, whether neutralized or not, was minor, however, compared to the independent influence of exercise in briefly constricting large airways.

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This Project Summary was developed by EPA's Health Effects Research Laboratory, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

The occurrence of oxidized sulfur compounds in the atmosphere is a well-known consequence of fossil fuel combustion and other industrial operations. Sulfuric acid (H_2SO_4) and its neutralization products [NH_4HSO_4 - $(\text{NH}_4)_2\text{SO}_4$] with ammonia (NH_3) are significant components of the submicrometer size particles in the atmosphere over large areas of North America and Europe. Inhalation of H_2SO_4 aerosol at 1 mg/m^3 for one hour in controlled human exposures affects mucociliary clearance rate. Inhalation of $(\text{NH}_4)_2\text{SO}_4$ at the same concentration has no effect. Similar exposures to H_2SO_4 have shown no changes in lung mechanical function, however.

There are many factors, physical and physiological, which when integrated contribute to the effects that inhaled acid sulfate compounds in particulate form will have on the respiratory system. Initial physical aerosol parameters such as chemical composition and particle size distribution are relatively easily controlled. These properties and the resultant magnitude and location of dose may be altered, however, by physiological parameters such as gaseous ammonia in the airways, elevated relative humidity (RH) and breathing parameters (e.g. frequency flow rate and tidal volume).

In animal exposures to sulfate compound aerosols, the sensitivity of lung mechanical functional measurements is critical to the assessment of effects.

The full report addressed three aspects that are of importance to the determination of health effects arising from the breathing of acid sulfate compounds in particulate form.

Measurements of Respiratory Ammonia and the Chemical Neutralization of Inhaled Sulfuric Acid Aerosol in Anesthetized Dogs

Sulfuric acid (H_2SO_4) and its neutralization products [NH_4HSO_4 - $(\text{NH}_4)_2\text{SO}_4$] with ammonia (NH_3) are important

components of the submicrometer-diameter particles suspended in the ambient atmosphere. Inhalation of H_2SO_4 aerosol at concentrations 1 mg/m^3 for one hour has been shown to affect mucociliary clearance rates in humans, whereas inhalation of $(\text{NH}_4)_2\text{SO}_4$ aerosol at the same concentration has no effect. It was hypothesized that during inhalation acid particles undergo neutralization by respiratory NH_3 as they course the upper airways. To the extent that it is the acidity of these particles that is irritating, acid neutralization by endogenous NH_3 during inhalation is important.

Also examined was the relationship between respiratory NH_3 and the chemical neutralization of inhaled H_2SO_4 aerosol in surgically isolated upper airways of anesthetized dogs.

It was shown that H_2SO_4 particles can undergo significant neutralization during inhalation via the nose or mouth by the time the particles pass the larynx. For a given flow rate, the percent neutralization depends both on NH_3 concentration and particle size, with $0.5 \mu\text{m}$ particles being neutralized more rapidly than $1.0 \mu\text{m}$ particles. Measurements of the rate of neutralization were in reasonable agreement with simple diffusion theory.

On the basis of chemical transformation occurring in the airways, the results suggest that smaller acid particles may be less irritating than larger ones and that inhalation via the nose is not necessarily more protective than via the mouth. These conclusions are tempered by the fact that the irritant potential of an acid particle is determined not only by its chemistry but also by its site of deposition. Nevertheless, these results can partially explain the results of Wolff and co-workers, who found that $0.9 \mu\text{m}$ H_2SO_4 particles are more irritating to dogs than $0.3 \mu\text{m}$ particles, but cannot help to explain the results of Amdur and co-workers, who found that $0.3 \mu\text{m}$ H_2SO_4 particles were more irritating to guinea pigs than the same concentration of $1.0 \mu\text{m}$ particles. In conclusion, neutralization of H_2SO_4 aerosol by airway NH_3 appears to be an important phenomena that can be studied by relatively simple techniques.

The Respiratory Response of Guinea Pigs to Aerosols. I Histamine Aerosol Control Study

The investigation of the potentially mild pulmonary functional responses in

guinea pigs to components of atmospheric aerosols requires an accurate description of both the aerosol under investigation (chemical species, mass concentration and size distribution of the droplet of particle, temperature, relative humidity) and of the animal preparation. The use of guinea pigs is confounded by intra- and inter-animal variability and small but important differences in protocols between laboratories which make comparisons difficult.

The full report describes the time course of pulmonary functional response in guinea pigs exposed to moderate concentrations of histamine aerosol, a known bronchoconstrictor. The aerosol parameters and the sensitivity of the guinea pig preparation are sufficiently well described to permit interlaboratory comparison. These results will provide a basis for a forthcoming paper on the analysis of pulmonary functional response data of guinea pigs that were exposed to aerosols of SO_2 and particulate sulfate compounds.

Female guinea pigs were monitored for dynamic lung compliance (C_{dyn}), pulmonary flow resistance (R_L), breathing frequency (f) and minute volume (V_{min}).

The only persistent change observed in any guinea pig exposure mode was the decrease in C_{dyn} at an aerosol concentration of $885 \mu\text{g/m}^3$ during the first exposure. Since all guinea pigs of that group displayed a decrease in C_{dyn} (statistically significant in nine of ten animals), the time course or response to this aerosol was examined. A progressive decrease in C_{dyn} which began within one minute, accompanied exposure to histamine. After 5-6 min, dispersion in the data increased. This can be explained, at least in part, by the large number of deep breaths observed. The average intra-animal coefficient of variation of C_{dyn} during control periods was 9% and the average inter-animal coefficient of variation of C_{dyn} was 30%. The large inter-animal variation adds dispersion to the data not related to observations on the time-course effect of histamine aerosol; this variation was eliminated by normalizing the data for each guinea pig.

The Influence of Exercise and Endogenous Ammonia on Pulmonary Irritation by Sulfuric Acid Aerosol

Recently a factor has been identified which may be of considerable impor-

tance in determining human response to inhaled acid particles. It has been shown that ammonia (NH_3) generated within the normal airways, and especially in the mouth, is capable of converting inhaled sulfuric acid to $(\text{NH}_4)_2\text{SO}_4$ or to NH_4HSO_4 and presumably reducing its irritant potency. Ammonia produced in the mouth is sufficient to convert up to $1500 \mu\text{g}/\text{m}^3$ H_2SO_4 to $(\text{NH}_4)_2\text{SO}_4$, a nearly neutral salt, provided that the acid particles remained in the mouth for a sufficient time. That this occurs while the acid particles traverse the mouth before entering the lower airways was not confirmed, but full conversion was found in exhaled particles. It was proposed that inhaled acid particles may not be fully neutralized before entering the lower airways under certain conditions, namely: during nose breathing because of lower NH_3 concentrations, and during rapid mouth breathing when particles encounter high NH_3 levels only briefly. Under these conditions, evidence of lower airways irritation might be expected, while during exposure with quiet mouth-breathing, no effect was anticipated.

To test a part of this hypothesis, human subjects were exposed to sulfuric acid particles during mouth breathing while at rest and then while exercising. The particle concentration, particle size and exercise level were chosen so that neutralization in the mouth should not be complete during exercise, while at rest the conversion was expected to be more nearly complete. Lung mechanical function was determined before and after exposure both at rest and with exercise.

The acute irritant potency of H_2SO_4 aerosol, in concentrations of $500 \mu\text{g}/\text{m}^3$ or more, is virtually undetectable in normal adults by usual measures of lung mechanical function. A more site-specific test, density dependence of maximum flow, provided evidence of very mild small airways constriction, but the work of others shows that measurement of tracheobronchial clearance is a much more sensitive indicator of response to H_2SO_4 . Mechanical changes were slight or absent even under conditions strongly unfavorable for neutralization of H_2SO_4 by endogenous NH_3 . Thus the influence of NH_3 conversion on lung function, if any, must be assessed by a method which is more sensitive than the ones used here. Subjects with known airway hypersensitivity, such as asthmatics, may provide a better means

for testing the hypothesis, as might the use of a functional test such as clearance rate.

D. Covert, M. Morgan, T. Larson, N. Frank, N. Horike, and D. Holub are with the University of Washington, Seattle, WA 98195.

Milan Hazucha is the EPA Project Officer (see below).

The complete report, entitled "Interaction of Acid Sulfates and the Respiratory System," (Order No. PB 81-190 498; Cost: \$6.50, subject to change) will be available only from:

*National Technical Information Service
5285 Port Royal Road
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*The EPA Project Officer can be contacted at:
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